Remarks

The Office Action of June 29, 2005 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is earnestly requested. Claims 1-16 are pending in the application, claims 1 and 9 being amended and new claims 15-16 being added by this response. The amendment of claim 1 is supported throughout the specification (see, *e.g.*, Examples 2 and 4). The amendment of claim 9 and new claims 15-16 are supported by the original claims and throughout the specification. No new matter has been added, and no excess claims fee is due.

In view of the foregoing amendments and following remarks, favorable reconsideration and withdrawal of the outstanding rejections are respectfully requested.

Priority

Applicant respectfully acknowledges the statutory requirement for a certified copy of the priority document. Applicant is in the process of obtaining the certified copy of the priority application from the Philippines patent office and will file the certified copy upon receipt thereof.

Objection to the Claims

Claim 9 was objected to as being in improper multiple-dependent format.

Claim 9 is hereby amended to overcome the rejection. Reconsideration and withdrawal of the objection are therefore respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-12 and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Deutsch *et al.* (U.S. Pat. No. 4,897,270) in view of Amey *et al.* (U.S. Pat. No. 6,080,426).

Claim 13 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Deutsch *et al.* (U.S. Pat. No. 4,897,270) in view of Amey *et al.* (U.S. Pat. No. 6,080,426), and further in view of Xiping Wang (U.S. Pat. No. 6,482,432).

Applicant respectfully submits that the foregoing rejections are overcome by the amendment of claim 1. Reconsideration and withdrawal of the obviousness rejections of claims 1-14 are therefore earnestly requested.

More particularly, the Examiner maintains that Deutsch *et al.* teaches providing a pharmaceutical tablet of cefuroxime axetil and the desirability of providing a film coat on the

tablet to mask the bitter taste. The Examiner acknowledges that Deutsch *et al.* does not teach providing the tablet in a capsule or the composition of the capsule. However, the Examiner asserts that Amey *et al.* teaches a process for encapsulation of caplets in a capsule, and therefore concludes that a person of ordinary skill in the art at the time of the invention would have been motivated to provide the cefuroxime axetil tablet of Deutsch *et al.* in the capsule of Amey *et al.*, with the expectation of providing a suitable dosage form having a neutral, non-bitter taste, as well as other benefits.

Applicant respectfully disagrees, and maintains that the claims 1-14, as amended, are patentable over Deutsch *et al.* and Amey *et al.*, individually and in combination, for the reasons set forth below.

In determining obviousness, the basic issue is whether applied references, alone or in any combination, suggest the claimed invention as a solution to the specific problem solved. When the prior art itself does not suggest or render obvious the claimed solution to that problem, the art involved does not satisfy the criteria of 35 USC § 103 for precluding patentability. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. Carela v. Starlight Archery, 231 USPQ 644 (Fed. Cir. 1986).

When features of prior art references are combined to establish obviousness, the mere possibility of such a combination does not render the result of that combination obvious absent a logical reason of record which justifies the combination. In re Regel, 526 F.2d 1399, 188 USPQ 136 (CCPA 1975). Instead, references may only be modified when (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or perform the claimed process, and (2) that those of ordinary skill in the art would have a reasonable expectation of success of making the claimed composition or performing the claimed process. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Thus, there must be a reason apparent to one skilled in the art at the time of the invention for applying the teaching at hand, or the use of the teaching as evidence of obviousness entails prohibited hindsight. Graham v. John Deere Co., 383 US 1, 148 USPQ 459 (1966); In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

Based on the foregoing case law, and according to MPEP 2143, three basic criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references

when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure, as such would be indicative of impermissible hindsight.

Thus, to establish a *prima facie* case of obviousness, the Examiner is required to cite a combination of prior art that not only teaches each and every element of the rejected claims, but also is required to cite substantial evidence to support the conclusion that one of ordinary skill in the art would be motivated to combine or modify the references as suggested, as well as substantial evidence that one of ordinary skill in the art would have a reasonable expectation of success in making the cited combination or modification.

The Combination of Deutsch *et al.* and Amev *et al.*
Does Not Teach or Suggest Each And Every Element of Applicant's Claim 1

Applicant's claim 1, as amended, recites a core tablet of cefuroxime axetil inside a capsule having a rupture time of **more than forty seconds**. Deutsch *et al.* does not disclose, teach or suggest a tablet of cefuroxime axetil inside a capsule having a rupture time of more than forty seconds. Rather, Deutsch *et al.* teaches a formulation of cefuroxime axetil with a film coating having a rupture time of **less than forty seconds**. Indeed, an important teaching of Deutsch *et al.* is that the film coating must rupture in less than forty seconds for the formulation to be effective, because the prior art teaches that a longer rupture time leads to gel formation and poor disintegration and hence dissolution of the antibiotic.

The characteristic tendency to form a gelatinous mass in contact with water is unique to cefuroxime axetil. Therefore, in formulating a solid format of cefuroxime axetil, one must not only provide a barrier layer to protect against bitterness, but must also make sure that the barrier layer does not induce gel formation by rupturing too slowly. Deutsch *et al.* teaches that a coated tablet of cefuroxime axetil must combine two critical components to prevent gel formation: i) a thin film-coating with a **rupture time of less than 40 seconds**; and ii) an effective amount of disintegrant to produce tablet core disintegration immediately following film coat rupture. Deutsch does not disclose or teach any solid oral format of cefuroxime axetil that does not gel when the protective taste masking barrier layer has a rupture time greater than 40 seconds.

The cefuroxime tablet of Deutsch *et al.* with a film-coat rupture time of less than 40 seconds may not provide an adequate barrier for taste-masking the bitterness of the drug, but the

thickness of this barrier layer cannot be increased further, as taught by Deutsch *et al.*, without causing gel formation of the tablet core, even if the tablet core contains a high level of disintegrant. Thus, the prior art teaches that the rupture time cannot exceed forty seconds, and therefore the prior art does not disclose or teach any solid oral format of cefuroxime axetil that does not gel when the protective taste masking barrier layer has a rupture time greater than 40 seconds.

Amey *et al.* does not cure the deficiencies of Deutsch *et al.*, rather Amey *et al.* merely teaches a process for encapsulation of caplets in a capsule by cold-shrinking. The objective of Amey *et al.* is to provide a tamper-proof solid format: "The solid dosage form according to the present invention is tamper-proof in that the caplet contained in the capsule cannot be removed from the capsule without destroying same (capsule)" (column 2, lines 19-22). Amey *et al.* further teaches: "According to a specifically preferred embodiment of the present invention, the clearance of the capsule shell and the caplet is in the range of from about 0 to about -0.5mm, which means that the caplet is compressed in the capsule" (column 2, lines 50-54).

Wang also does not cure the deficiencies of Deutsch *et al.* and Amey *et al.*, rather Wang merely teaches vegetable based capsules. Wang does not disclose or teach any solid oral format of cefuroxime axetil which does not gel when the protective taste masking barrier layer has a rupture time greater than 40 seconds. Therefore, it is respectfully submitted that Applicant's claims cannot be obvious over Wang standing alone or in combination with Deutsch *et al.* and Amey *et al.*

Applicant's invention provides a core tablet containing the antibiotic cefuroxime axetil inside a capsule, which serves to mask the bitter taste of the drug. Applicant has unexpectedly found that, in contrast to the teachings of the prior art pertaining to the film-coated tablet of cefuroxime axetil (*i.e.*, Deutsch *et al.*), Applicant's tablet-in-a-capsule format does not result in gel formation of cefuroxime axetil, even if the rupture time of the taste masking barrier (capsule) is significantly longer than the forty (40) second time limit for the film-coated tablet of cefuroxime axetil. The longer rupture time of Applicant's tablet-in-a-capsule improves taste masking without sacrificing dissolution of cefuroxime axetil. The prior art teaches that the rupture time cannot exceed forty seconds, and therefore the prior art teaches away from the claimed invention.

Capsules are widely used in the pharmaceutical industry as both carrier and barrier layer for drugs, whereby the drugs are normally filled into capsules as granules or powders. Capsules have good barrier protection against bitterness because their disintegration time is long. As shown in Attachment I, commercial gelatin and hydroxypropylmethylcellulose capsules have *in vitro* disintegration time in excess of 130 seconds, while pullulan polysaccharide capsule, the fastest, has a disintegration time of about 87 seconds. However, these *in vitro* disintegration times translate to very long *in vivo* disintegration time (Attachment 1), determined through gamma scintigraphy, of 8 minutes for gelatin capsules, 28 minutes for hydroxypropylmethylcellulose capsules, and 9 minutes for pullulan polysaccharide capsules.

Despite the actual very long *in vivo* disintegration time, Applicant's invention is bioequivalent to the commercial product based on the patent to Deutsch *et al.* (Glaxo's Ceftin, see Example 4 of Applicant's patent application). Clearly, from the teaching of Deutsch *et al.*, a person of ordinary skill in the art would not consider using commercial capsules as barrier layers for cefuroxime axetil, because their rupture time is significantly longer than 40 seconds, a rupture time for film coating that Deutsch *et al.* teaches to cause gel formation of the core cefuroxime axetil tablet. Moreover, a person of ordinary skill in the art would not be motivated to put a core antibiotic tablet inside a capsule, because it is easier to simply fill the antibiotic as granules, without tabletting, into the capsule. Indeed, Applicant is aware of no commercial antibiotic that is sold anywhere in the world as a tablet-in-a-capsule.

As the examples in Applicant's patent application show, cefuroxime axetil filled as granules into capsules, as a person of ordinary skill in the art would do for antibiotic capsules, results in gel formation of the cefuroxime axetil and hence poor dissolution. However, Applicant has unexpectedly discovered that, by tabletting the same formulation of cefuroxime axetil granules and filling into capsules as tablets, gel formation does not occur, even if the mean rupture time (as in our examples) is about 180 seconds. These unexpected results of Applicant's experiments are not taught or suggested by the prior art, indeed, the prior art of record teaches away from Applicant's results.

Furthermore, there is no teaching in the prior art of record that one of ordinary skill in the art would be motivated to modify Deutsch *et al.*, or would have a reasonable expectation of success in modifying Deutsch *et al.*, as suggested by the Examiner. Deutsch *et al.* clearly requires that the barrier film layer for taste masking of a cefuroxime tablet must rupture in less

than 40 seconds, even if the core tablet contains high levels of disintegrant, to prevent gel formation which impairs dissolution. A person of ordinary skill in the art would not, based on this teaching, take the core tablet of Deutsch *et al.* and use a capsule as a barrier film layer for taste masking, considering that commercially available capsules are known to have long rupture times significantly in excess of 40 seconds (see Attachment 1). Moreover, Deutsch *et al.* does not disclose all of the elements of the Applicant's Claim 1. In short, Deutsch *et al.* does not disclose or teach any solid oral format of cefuroxime axetil whose protective taste masking barrier layer has a rupture time greater than 40 seconds and yet does not cause gel formation.

Furthermore, if a capsule is the desired format, a person of ordinary skill in the art would simply take antibiotic granules, without tabletting, to fill directly into capsules for taste masking. It is highly unusual and therefore non-obvious to take the extra steps of tabletting the antibiotic and then filling the tablet into capsule (a difficult operation commercially), if the objective is simply taste masking. However, as shown in the examples of the present application, filling cefuroxime axetil granules directly into capsules, even with high levels of disintegrant, still results in gel formation and hence poor dissolution.

In addition, Amey *et al.* does not disclose or teach any solid oral format of cefuroxime axetil that i) is not cold-shrunk; and ii) does not gel when the protective taste masking barrier layer has a rupture time greater than 40 seconds. In short, there is nothing in the prior art that would lead one of ordinary skill to combine Deutsch *et al.* and Amey *et al.* as suggested by the Examiner, and there is no reasonable expectation of success, particularly since Deutsch *et al.* clearly specifies a rupture time of less than 40 seconds for the barrier film layer to prevent gel formation.

It is respectfully submitted that the obviousness rejection of claim 1 is thus overcome. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Dependent claims 2-14, being dependent upon and further limiting independent claim 1, should be allowable for that reason, as well as for the additional limitations recited therein. Reconsideration and withdrawal of the rejection of claims 1-14 as being obvious are therefore respectfully requested.

Conclusion

Based upon the above amendments, remarks and the papers of record, Applicant believes that the pending claims of the above-captioned application are in allowable form and patentable over the prior art of record. Applicant respectfully requests reconsideration of the pending claims 1-16 and a prompt Notice of Allowance thereon.

Please direct any questions or comments to Thomas T. Aquilla at (607) 227-4428.

Respectfully Submitted:

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Dated: September 29, 2005